EXHIBIT A

Neurontin Action Plan – PDA2-2004

2004 Goal

- National Goal = Achieve $2.5 Billion and 15% growth in 2004
- Currently 104% of Budget, GAR = 98.77%. YTD Sales of $780 million with growth 19.7%

Market Overview

- Neurontin weekly shares are trending up - bottomed in January after declining in 2003.
- Tablet business has increased from 32% to 37% of Neurontin total.
- 75% of targeted PCPs now achieving at least 1800mg. PCPs still slowest to get there.
- Other AEDs growing faster than Neurontin in LTC (16% vs 59%)
- Eisai's new specialty team will promote Zonegran.

Strategies

- 2nd position Detail on every call
- Deliver Consistent 3 Step Message
- Grow LTC business

No calls on Psychs!!!!

Core Message

"NEURONTIN Is a Different Kind of Medication that provides Significant Reduction of the *Burning*, *Stabbing*, and *Electric-Shock-Like* Pain of PHN, when dosed up to 600mg TID or Pain Free"

Messaging

1) Differentiate Neuropathic pain from Joint/Muscle pain - Describe PHN as one type of Neuropathic pain
2) Neurontin is most effective for relieving the pain of PHN
   a. Sell Rice & Robotham
   b. Sleep improvements due to pain reduction – esp in LTC
3) Titrate to 600mg TID or Pain Free utilizing scored tablets.

Executional Excellence

- Roll out LTC Kits – set specific metrics for appropriate LTC areas.
- Roundtable programs, Conference Calls
- Re-N-Force letters

NEURONTIN POA II DETAIL:

PAGE 1:
"When you have a patient with the *Burning, Stabbing, or Electric-Shock-Like Pain* of PHN, use Neurontin tablets FIRST by dosing up to 600mg TID or Pain Free. (differentiate between nociceptive here)

PAGE 2:
In fact, Neurontin is the only oral medication indicated for PHN—one of the most debilitating forms of neuropathic pain. Neurontin received this indication only after proving efficacious in two pivotal trials for PHN. Patients in both studies showed significant reductions in pain scores by week one and on average a 2.3 reduction in pain scores—that could well be the difference between being able to get up and out the door and staying in bed all day doctor. In addition, please note that half of the patients in Rice study had failed three other treatment therapies before being prescribed Neurontin. These patients are in severe pain and for many of them failure is not an option.

Include pain-related sleep interference here also.

No other oral medication has been able to achieve similar results to date doctor—and be assured that others have tried.

PAGE 3:
Since Neurontin is the only oral agent with demonstrated efficacy in the PHN patient and since most PHN patients would rather avoid failed therapy options, doesn't it make sense to start with Neurontin and to titrate Neurontin tablets to 600mg TID in all of your PHN patients?

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On Drugs and Therapeutics

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April 12, 2004

GABAPENTIN *(NEURONTIN)* FOR CHRONIC PAIN

Gabapentin (*Neurontin* - Pfizer), which has been available in the US since 1994, is approved by the FDA only for treatment of partial epilepsy and postherpetic neuralgia, but is widely used off-label for a number of other indications, especially neuropathic pain syndromes. According to one report, among Medicaid recipients in Florida receiving gabapentin, 71% of prescriptions were for chronic pain and 8% for seizures and neuralgia ("The Pink Sheet" February 2, 2004; 66:30).

TREATMENT OF CHRONIC NEUROPATHIC PAIN — Neuropathic pain (originating in the peripheral or central nervous system) usually responds poorly or not at all to NSAIDS or acetaminophen (*Tylenol*, and others) and does not respond as well as other types of pain to standard doses of opioids. Anticonvulsants are often used for treatment of chronic neuropathic pain, but the only pain-related indications approved by the FDA for these drugs are trigeminal neuralgia (carbamazepine) and postherpetic neuralgia (gabapentin). Tricyclic antidepressants such as amitriptyline (*Elavil*, and others) and desipramine (*Norpramin*, and others) can relieve many types of neuropathic pain, but they cause anticholinergic effects and orthostatic hypotension, particularly in elderly patients, and are not recommended for patients with ischemic heart disease. A 5% lidocaine patch *(Lidoderm)* and tramadol *(Ultram)*, a centrally acting analgesic, have also been reported to be effective (RH Dworkin et al, Arch Neurol 2003; 60:1524).

MECHANISM OF ACTION — Gabapentin is an analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Its mechanism of action in pain relief is unclear. The drug binds to specific subunits of voltage-sensitive calcium channels in the spinal cord, which may interfere with transmission of noxious stimuli.

EFFICACY FOR TREATMENT OF NEUROPATHIC PAIN — Postherpetic neuralgia – In a randomized, double-blind 8-week trial, average daily pain scores decreased by 33.3% in 113 patients with postherpetic neuralgia taking 1200-3600 mg/d of gabapentin, compared to a 7.7% reduction in 116 patients taking placebo (M Rowbotham et al, JAMA 1998; 280:1837). Another randomized double-blind trial compared gabapentin 1800 or 2400 mg/d to placebo in 334 patients with postherpetic neuralgia. After 7 weeks of treatment, reductions in pain scores from baseline were 34.5% and 34.4% for the 1800-mg and 2400-mg doses of gabapentin versus 15.7% for placebo, a statistically significant difference (AS Rice, S Maton et al, Pain 2001; 94:215).

Painful diabetic neuropathy – In a randomized, double-blind, 8-week trial, in 165 patients with diabetic peripheral neuropathy, mean pain scores were significantly lower with gabapentin (1800-3600 mg/d) compared to placebo from weeks 2-8. About 60% of patients treated with

gabapentin had at least a moderate improvement in pain scores, compared to 33% of those who took placebo (M Backonja et al, JAMA 1998; 280:1831). A small randomized, double-blind, crossover trial compared gabapentin 900 to 1800 mg/day with a relatively low dose of amitriptyline, 25 to 75 mg/day, for treatment of diabetic peripheral neuropathy pain. After 6 weeks, 11 (52%) of 21 patients treated with gabapentin achieved moderate or greater pain relief compared to 14 (67%) of 21 treated with amitriptyline; this difference was not statistically significant (CM Morello et al, Arch Intern Med 1999; 159:1931).

Other Pain Syndromes – Therapeutic benefit has been reported after off-label use of gabapentin for other neuropathic pain syndromes, including trigeminal neuralgia, multiple sclerosis pain, neuropathic head and neck pain, HIV-related sensory neuropathy, phantom limb pain, Guillain-Barré syndrome, complex regional pain syndrome and pain associated with spinal cord injury. These reports were mostly sponsored and, according to some sources, written by the manufacturer (MG Serpell et al, Pain 2002; 99:557; I La Spina et al, Eur J Neurol 2001; 8:71; A Mack, J Manag Care Pharm 2003; 9:559). In one study, gabapentin interacted synergistically with opioids in patients with cancer pain (MI Bennett and KH Simpson, Palliat Med 2004; 18:5). In another, gabapentin given postoperatively decreased use of morphine, but did not affect pain scores (G Dierking et al, Acta Anaesthesiol Scand 2004; 48:322).

OTHER OFF-LABEL USES — A randomized, double-blind 12-week trial found that gabapentin titrated to 2400 mg/d was more effective than placebo in preventing **migraine** headaches. The median 4-week migraine rate at the end of the treatment period was 2.7 with gabapentin and 3.5 with placebo, compared to 4.2 and 4.1 at baseline. A reduction of at least 50% in the 4-week migraine rate was observed in 26 of 56 (46%) gabapentin-treated patients compared to 5 of 31 (16%) treated with a placebo (NT Mathew et al, Headache 2001; 41:119).

Small open-label trials and case reports have suggested that gabapentin is effective for treatment of both depression and mania in bipolar disorder. However, controlled trials in patients with refractory **mood disorders** found that gabapentin alone or added to other drugs was less effective than lamotrigine (*Lamictal*), and no more effective than placebo (AE Evins, J Clin Psychiatry 2003; 64 suppl 8:9). In a small controlled trial, gabapentin was more effective than placebo in patients with **social anxiety disorder** (AC Pande et al, J Clin Psychopharmacol 1999; 19:341). Gabapentin has also been used for treatment of **attention deficit disorder**, but only a few case reports have been published.

ADVERSE EFFECTS — Common adverse effects of gabapentin are dizziness and somnolence, which usually occur more often during dose titration and resolve over time. Ataxia, fatigue, peripheral edema, confusion, depression and asthenia can occur. A withdrawal syndrome with anxiety, insomnia, nausea, pain and sweating has been reported after abrupt discontinuation of the drug.

DRUG INTERACTIONS — Gabapentin does not induce or inhibit hepatic microsomal enzymes. Antacids may decrease the bioavailability of the drug by about 20%.

DOSAGE AND COST — Gabapentin is marketed in 100-, 300- and 400-mg capsules and recently became available in 600- and 800-mg scored tablets. The recommended starting dosage for adults with postherpetic neuralgia is 300 mg on Day 1, 600 mg on Day 2 (divided b.i.d.), and 900 mg on Day 3 (divided t.i.d.). The dose can then be titrated up as needed for pain relief to a daily dose of 1800 mg (divided t.i.d.). To limit daytime sedation, some patients may need to start with 100 mg in a single dose at bedtime, which can be increased gradually over 3-8 weeks. In clinical studies of postherpetic neuralgia, efficacy was demonstrated for doses ranging from 1800 to

3600 mg/d (the usual dosage for epilepsy), but no additional benefit was shown at doses greater than 1800 mg/d. The dosage should be lowered for patients with renal insufficiency or on hemodialysis. One month's supply of the drug at a dosage of 1800 mg/day costs about $205.20, according to data from retail pharmacies nationwide provided by NDCHealth, a health care information services company, February, 2004.

CONCLUSION — Although FDA-approved only for treatment of partial epilepsy and postherpetic neuralgia, gabapentin *(Neurontin)* is widely used off-label, particularly for chronic pain. In short-term studies, it appears to be effective for painful diabetic neuropathy and might be useful for some other forms of neuropathic pain as well, and possibly for prophylaxis of migraine, but more controlled trials are needed. There is no good evidence that gabapentin is effective for mood disorders or attention deficit disorder. The drug can cause dizziness, somnolence and confusion, especially at higher doses.

PEMETREXED *(ALIMTA)* FOR MESOTHELIOMA

The combination of pemetrexed (*Alimta* – Lilly) and cisplatin is the first chemotherapy regimen approved by the FDA for treatment of malignant pleural mesothelioma. This uncommon malignancy, which has been linked to asbestos exposure, was previously considered unresponsive to chemotherapy, with a median survival of 6-8 months from diagnosis (VW Rusch, J Clin Oncol 2003; 21:2629).

PHARMACOLOGY — Pemetrexed is an antimetabolite that inhibits several enzymes involved in folate metabolism, including dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide formyltransferase (WT Purcell and DS Ettinger, Curr Oncol Rep 2003; 5:114). Following IV administration, the drug is cleared unchanged, primarily by the kidneys, with an elimination half-life of 3.5 hours.

CLINICAL STUDIES — Approval of pemetrexed was based mainly on the results of a randomized trial that included 448 chemotherapy-naïve patients with unresectable mesothelioma who were randomized to receive either pemetrexed plus cisplatin (*Platinol*, and others) or cisplatin alone. Patients treated with the combination had a statistically significantly longer median survival (12.1 vs. 9.3 months), a longer time to progression (5.7 vs. 3.9 months), and a higher overall response rate (41% vs. 17%) (NJ Vogelzang et al, J Clin Oncol 2003; 21:2636). Patients on the combination also showed improvement in pain, shortness of breath, and quality of life (RJ Gralla et al, Proc Am Soc Clin Oncol 2003; 22:621, abstract 2496). In 27 patients with mesothelioma, pemetrexed was also effective when combined with carboplatin (A Hughes et al, J Clin Oncol 2002; 20:3533). In a phase II trial of 64 patients taking pemetrexed as a single agent, the response rate was 14% and median survival was 10.7 months (GV Scagliotti et al, J Clin Oncol 2003; 21:1556).

Pemetrexed is under investigation for treatment of several other malignancies besides mesothelioma, including non-small cell lung, gastric, pancreatic, and breast cancer (GV Scagliotti and S Novello, Expert Opin Investig Drugs 2003; 12:853; E Bajetta et al, Ann Oncol 2003; 14:1543; HL Kindler et al, Proc Am Soc Clin Oncol 2002; 21:125a, abstract 499).

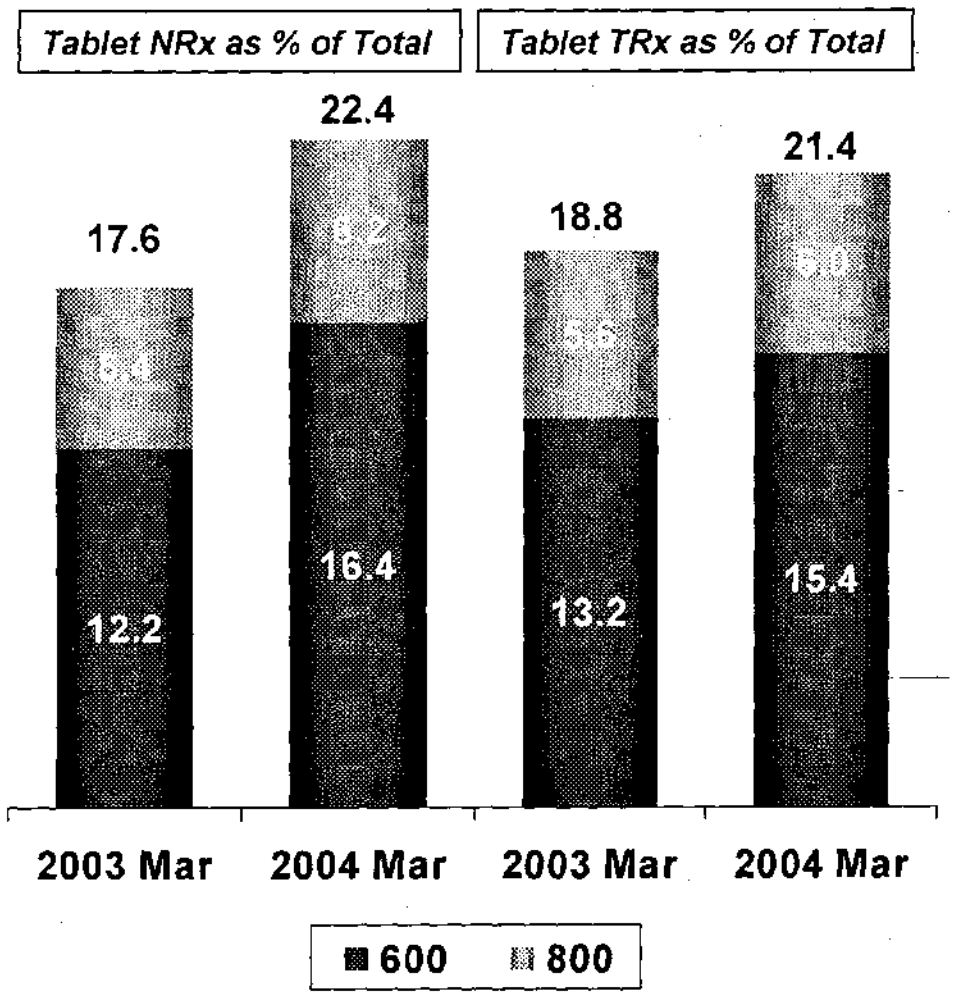
ADVERSE EFFECTS — The most common adverse effects of pemetrexed are myelosuppression, rash, fatigue, mouth sores, nausea and diarrhea. Supplementation with vitamin B12 (1000 µg IM q9 weeks) and folic acid (350-1000 µg PO daily), started one week before the first treatment, decreases toxicity with no apparent loss of efficacy (C Niyikiza et al, Semin Oncol 2002; 29 suppl 18:24). Patients should also take dexamethasone (4 mg b.i.d. x 3d) starting the

POA 2 Strategies and Initiatives

DO NOT DETAIL

NEURONTIN (gabapentin)

Demand for Tablets Growing with Dosing Message and Scored Tablet



Source: IMS March 2004

Scored Tablet News

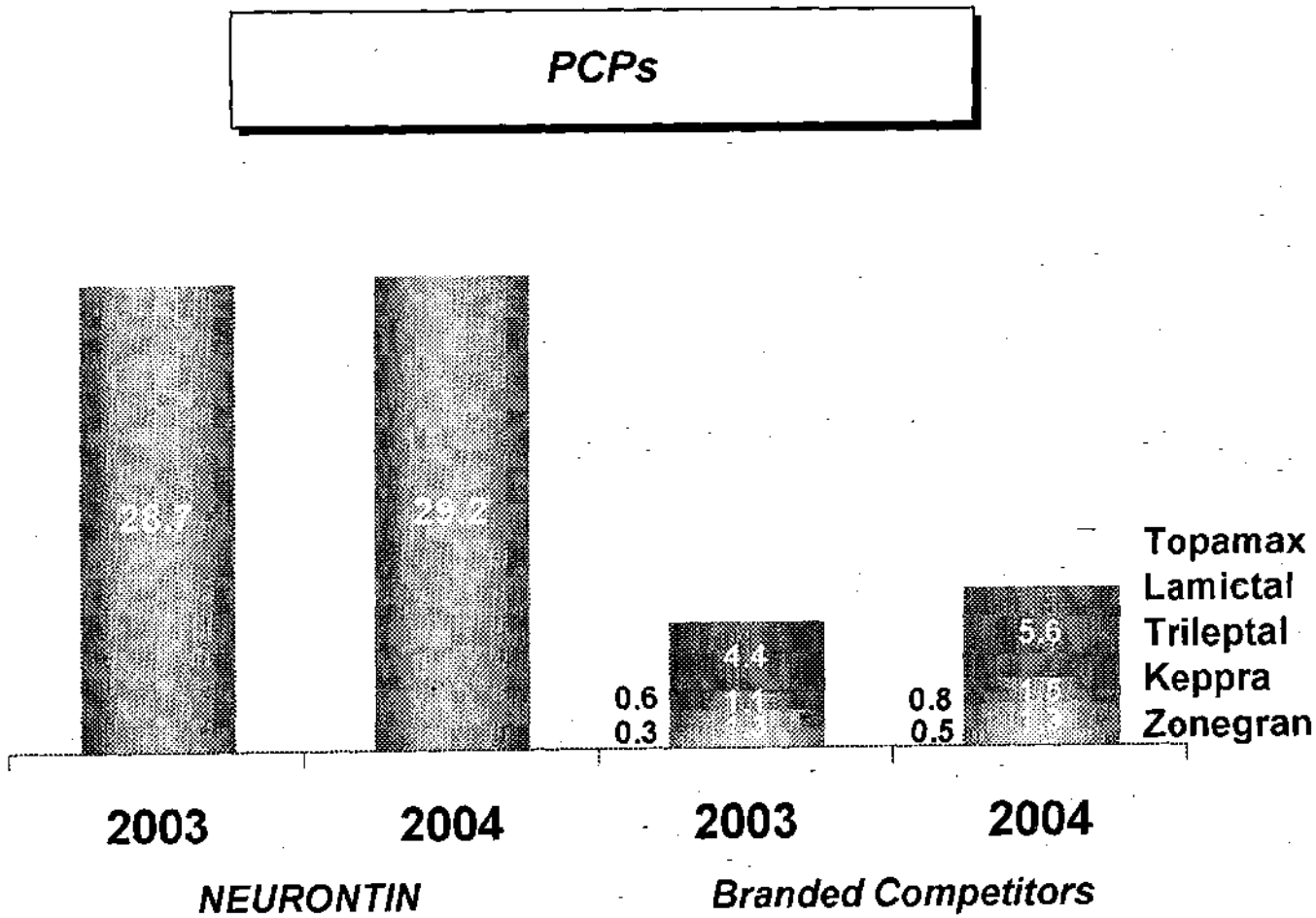
- Shipping Began February 2, 2004
- Scored Tablets Sales Are $244MM*
- Tablet Sales Are 38% of Total Sales, Up from 32%*

*Source: Internal Sales as of May 3, 2004

NEURONTIN (gabapentin)

NEURONTIN Market Share Among PCPs Continues to Rise

AED NRx Market Share (%)



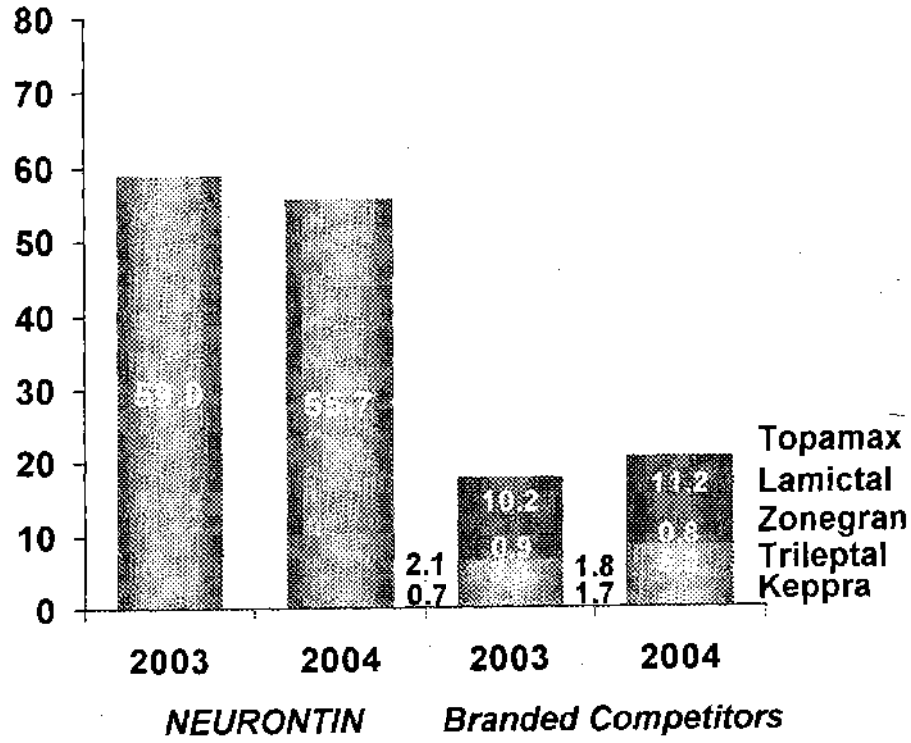
Source: IMS Health NPA; 1st Quarter, 2004

NEURONTIN (gabapentin)

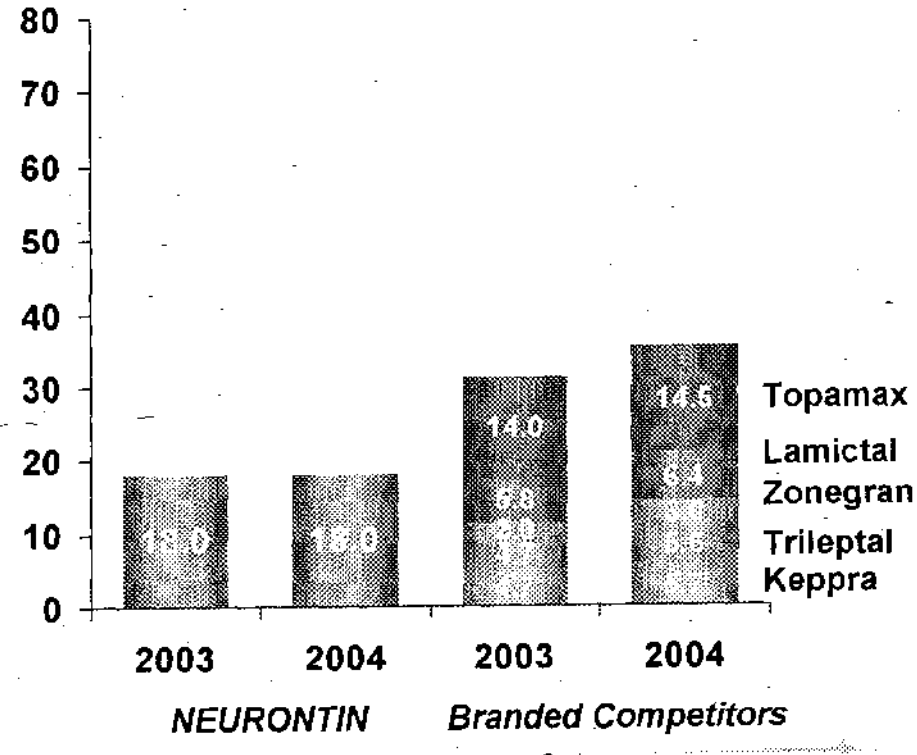
Competition Experiencing Robust Growth Among Specialists

AED NRx Market Share (%)

Anesthesiologists



Neurologists



Source: IMS Health NPA; 1st Quarter 2004

NEURONTIN (gabapentin)

Competitors Growing Among Neurologists in Non-PHN Markets

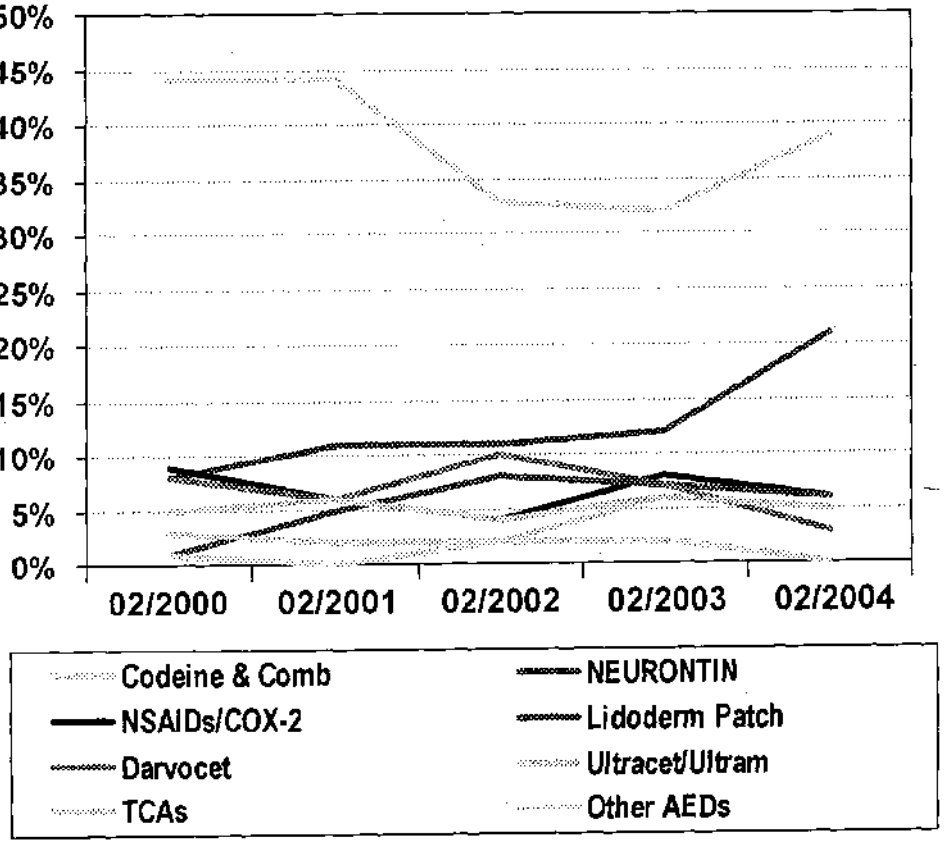
Market Research/Advisory Board Insights

- **Loss in Neurologist AED Market Share Is Concentrated in Off-Label Indications**
- **Changing PCP Referral Patterns May Be Leading to a Plateau in Neuro AED Market Share for PHN**
  - Smaller Percentage of Referrals Are NEURONTIN-Naïve
  - Most Referrals Reaching 1800mg/day
  - Neurologists Are Forced to Try Other AEDs to Treat PHN
- **Despite Growing Experience Base in Using Other AEDs to Treat PHN, NEURONTIN Remains the 1st Line Treatment of Choice by Neurologists**

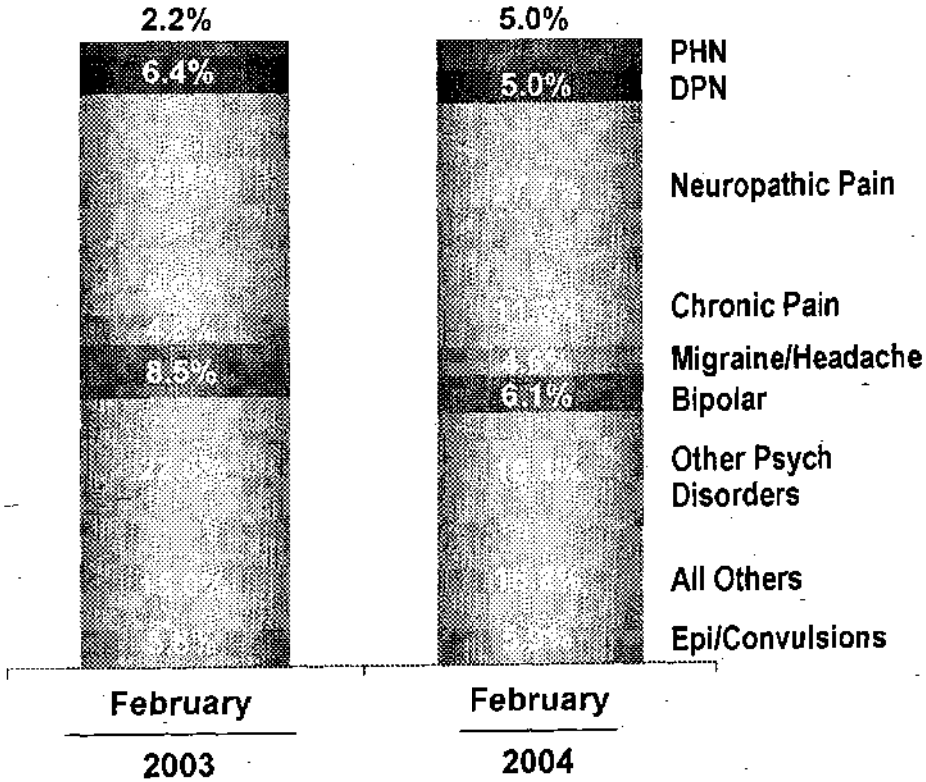
NEURONTIN (gabapentin)

NEURONTIN PHN Use Up Since Launch

Share of PHN Drug Uses



NEURONTIN Drug Uses

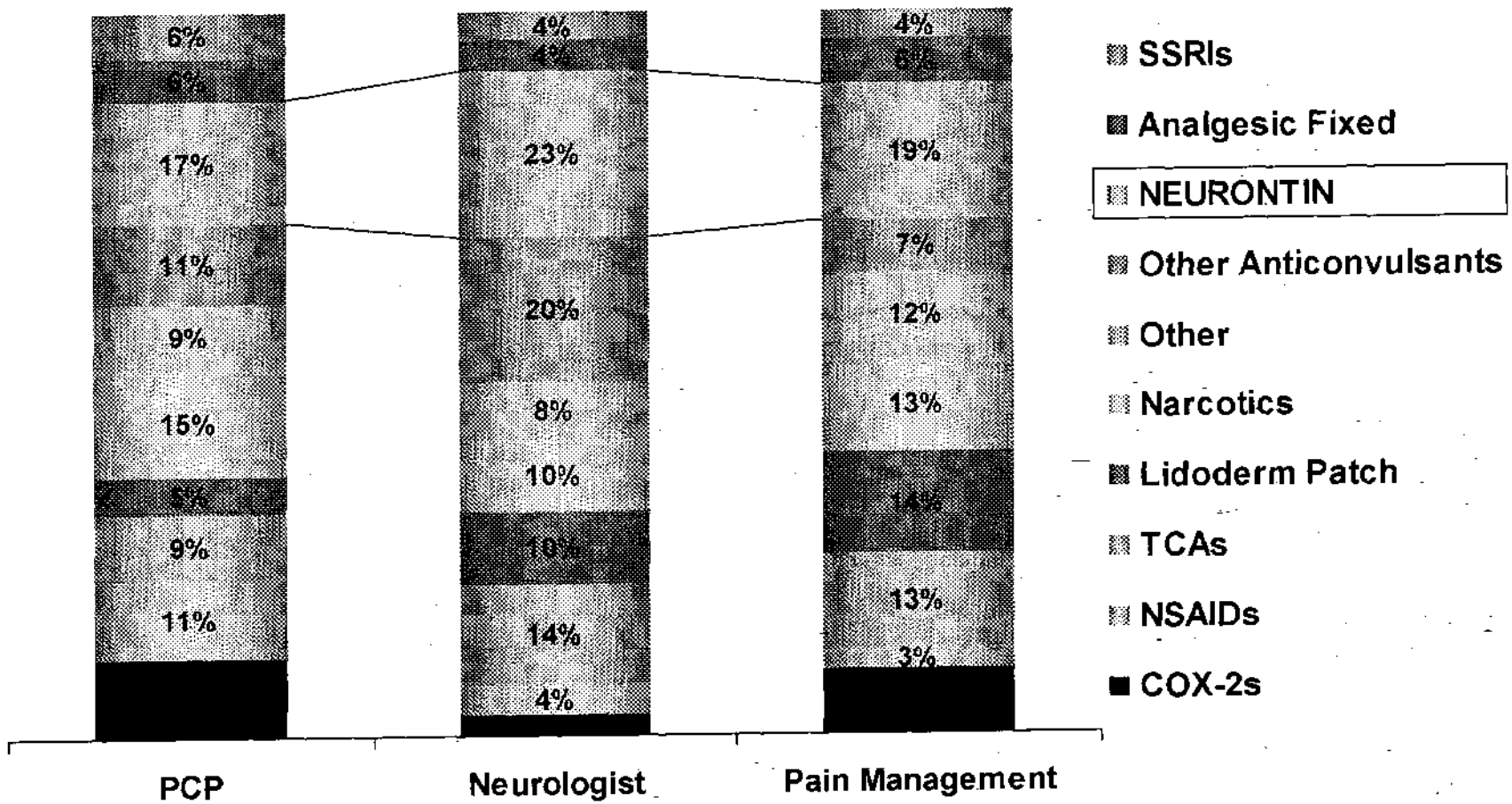


Source: Scott Levin PDDA; MAT February 2004

NEURONTIN (gabapentin)

Still Room for NEURONTIN in PHN

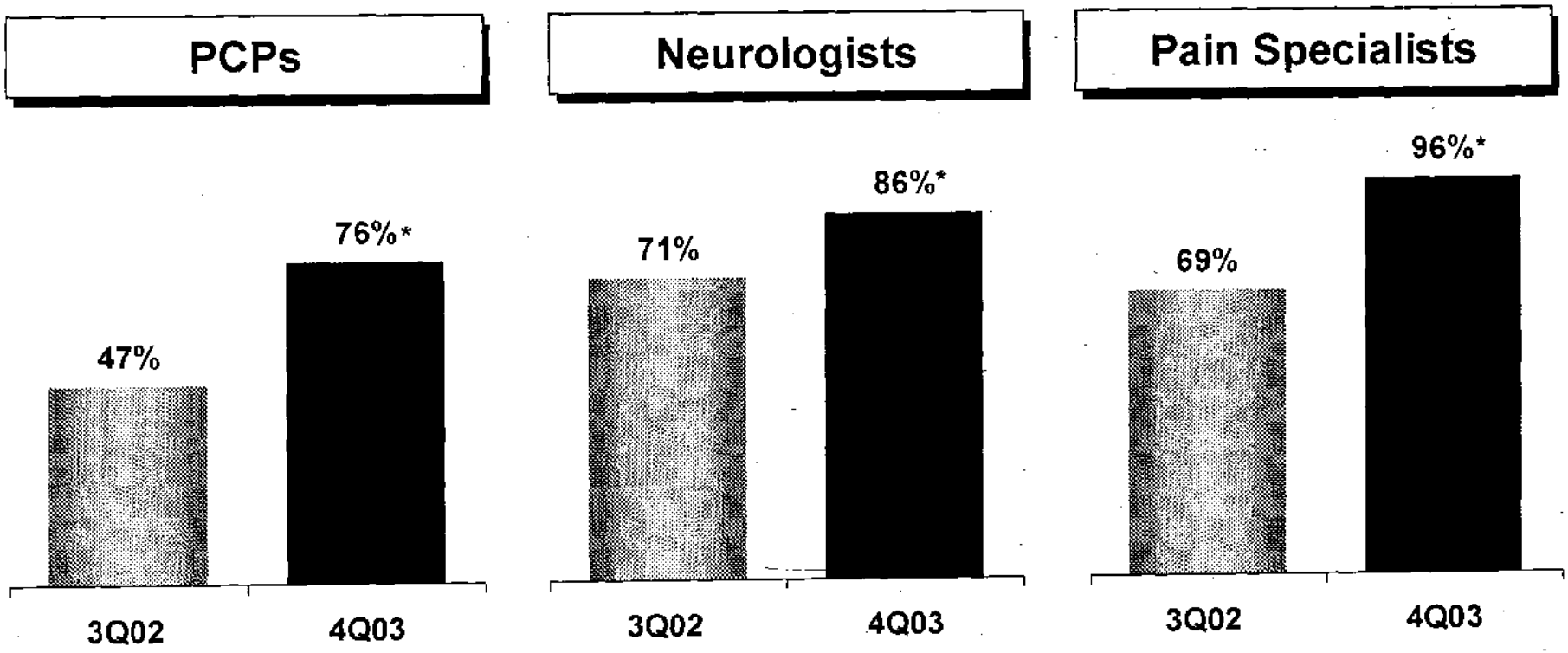
Agents Used in PHN



Source: Ziment PHN Tracking Study, December 2003

NEURONTIN (gabapentin)

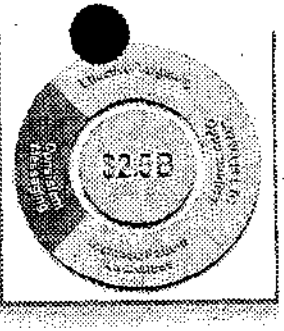
More Physicians Reaching Optimal Dose of 1800mg/day



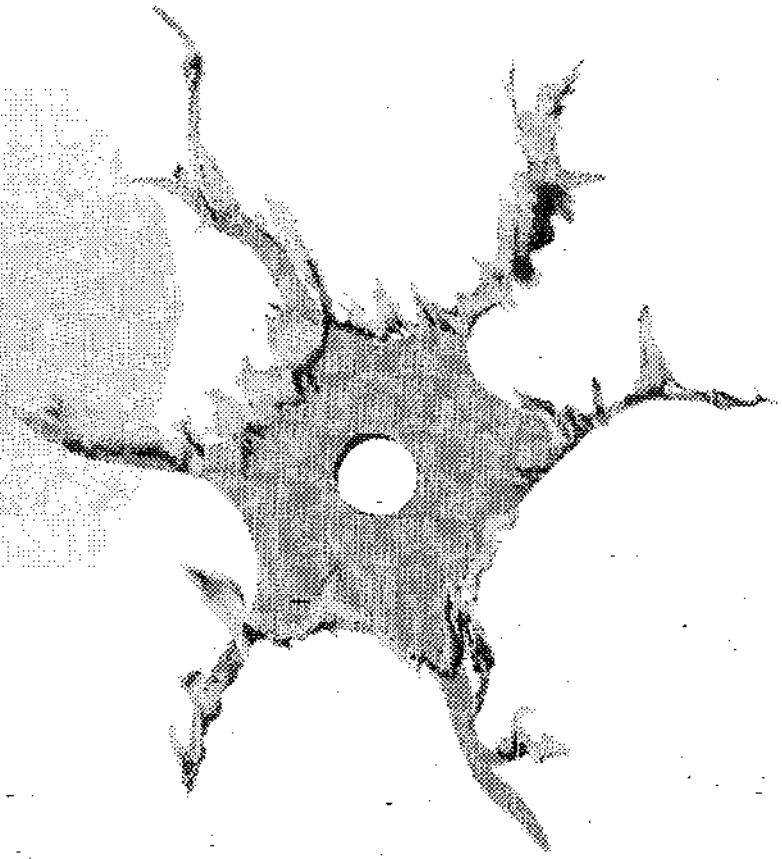
*Indicates Significant Difference from Previous Wave at 95% Confidence Level
Source: Ziment PHN Tracking Study, December 2003

NEURONTIN (gabapentin)

NEURONTIN GC Core Message



"When you have a patient with the ***Burning, Stabbing, or Electric-Shock-Like Pain*** of PHN, **Use Neurontin FIRST -** dosing up to 600mg TID or to Pain Free



A-TEAM

NEURONTIN (gabapentin)

NEURONTIN
Key Competitive Advantages

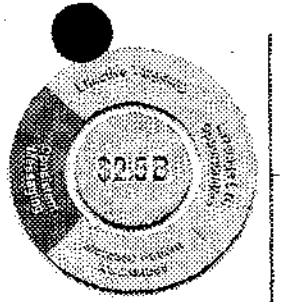
- Favorable Safety and Tolerability Profile
- Not Hepatically Metabolized or Protein Bound
- Few Drug-Drug Interactions
- Does Not Require Blood Level Monitoring or Liver Function Testing
- No Contraindications

  (Except in Patients Who Have Demonstrated Hypersensitivity to the Drug or Its Ingredients)

Implications: ***Safe and Easy***

NEURONTIN (gabapentin)

3-Step Messaging Consistently Communicates the Core Message



- ***Differentiate*** **Between Neuropathic and Musculoskeletal (Nociceptive) Pain by Highlighting Symptoms**

- **Drive Home *Efficacy* at 600mg TID**
  - Significant PHN Pain Reduction as Early as Week 1 in 2 Pivotal Trials
  - Significant Improvement in Patient-Reported Outcomes
  - Significant Reduction in "Pain-Related" Sleep Interference

- **Reinforce *Dosing***
  - Up to 600mg TID or Pain Free
  - New 3x3 Dosing Option to Simplify Titration
  - Introduce Scored Tablets

Visual Aid

NE170280

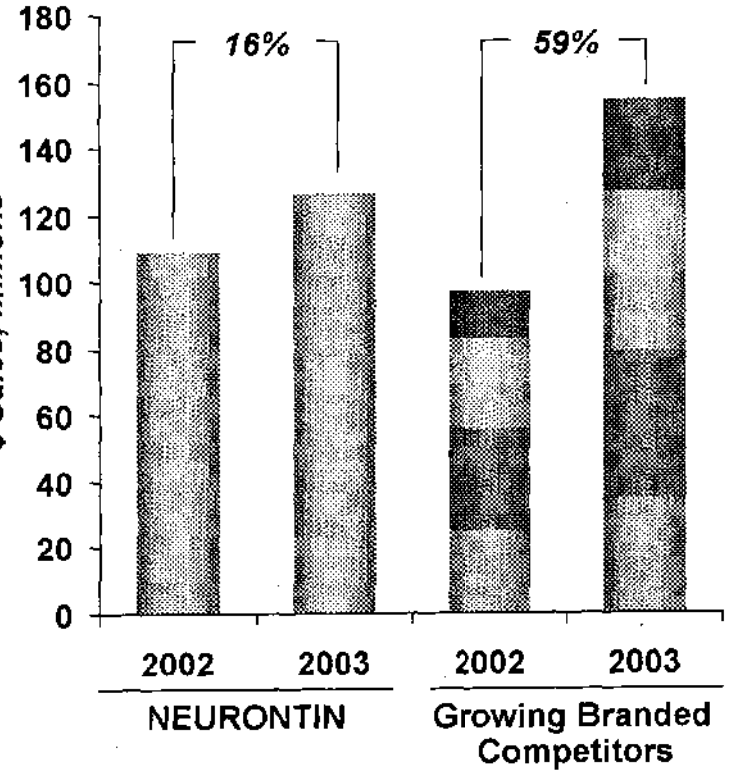
Pocket Guide

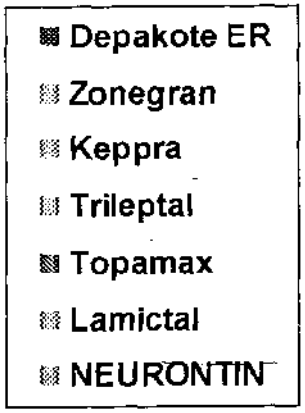
NE170262

NEURONTIN (gabapentin)

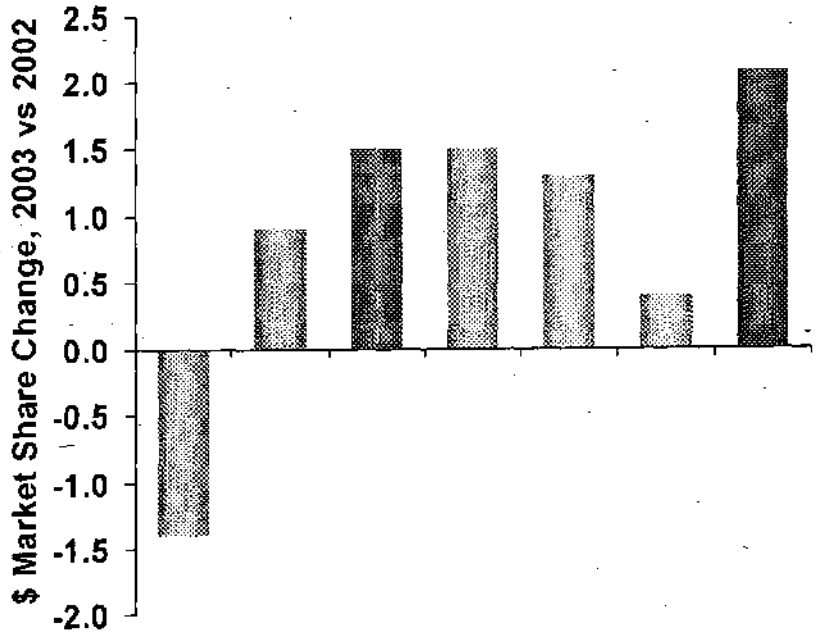
Competition Outpacing NEURONTIN In a Growing LTC Business

NEURONTIN Growing at 16% But Outpaced by Competitors





Market Share Eroded by Smaller Players



Source: IMS 2002 and 2003 Full Year Sales, LTC National Sales Perspective

NEURONTIN (gabapentin)

Get a Handle on PHN: LTC In-Service Kit

- Comprehensive, Disease-Management Program for Use with LTC Customer
- Deliver to DON or Medical Director
- In-Service Audience: LTC Staff
- In-Service Will Help:
  - Raise Awareness of PHN
  - Highlight Pain Differentiation
  - Reinforce Accurate Diagnosis
  - Promote Effective Treatment of PHN with NEURONTIN
- Allocation: 15 per PD2 Representative
- Backgrounder Available Separately for Ordering

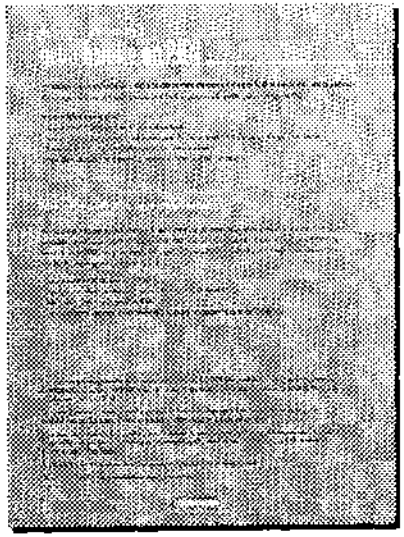
NE169291

NE169291F

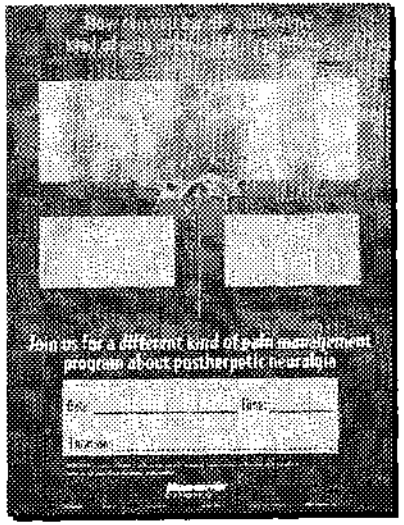
Kit in OOAK Is a Sample Only

NEURONTIN (gabapentin)

Invitation Material Helps Introduce and Organize a Successful In-Service



Sell Sheet



Announcement Poster

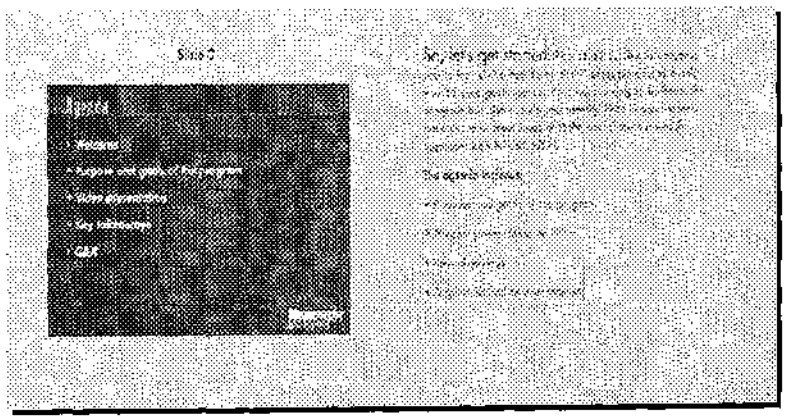
Provide Customer with

- Overview of Program
- Key Benefits for Organizations

- Generates Interest in PHN
- Invites Staff to Attend In-Service Meeting

NEURONTIN (gabapentin)

Presentation Materials for an Effective In-Service Program



Discussion Guide

- **For the Meeting Leader**
- **Designed to Complement the Video Presentation**
- **PowerPoint Slides and Speaker Notes**

Short Video Presentation That Addresses

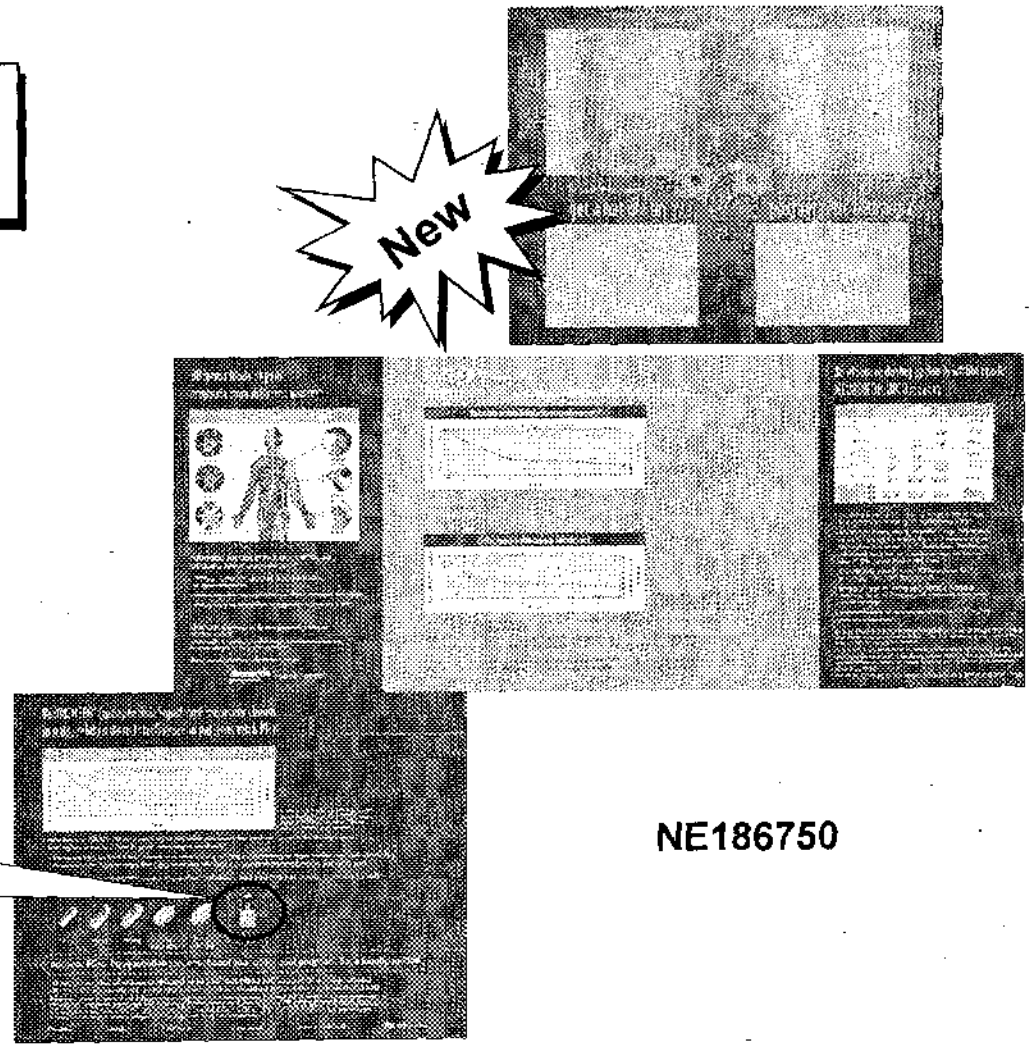
- **Impact of PHN in Elderly Patients**
- **Need to Focus on Accurate Diagnosis and Treatment of PHN**
- **Patient and Nurse Testimonials**
  - Featuring PHN Patients Rue McClanahan and Husband Morrow Wilson
- **Treatment with NEURONTIN**

NEURONTIN (gabapentin)

LTC Sell Sheet Emphasizes 3-Step Message with LTC Branding

Leave Behind That Delivers 3-Step Message

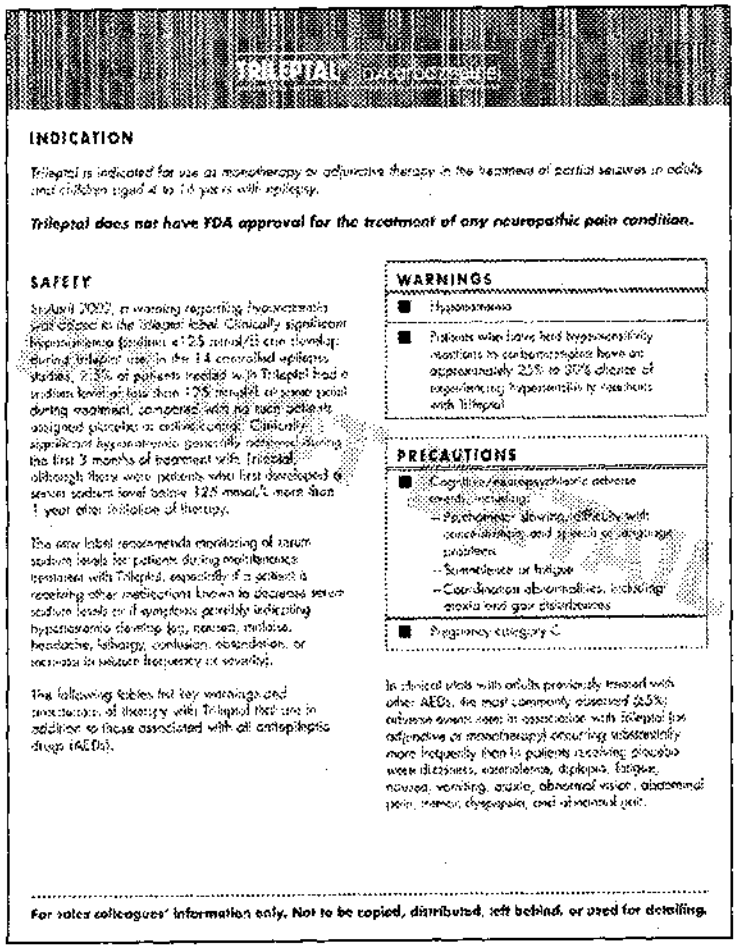
- **Differentiation (Left Panel)**
- **Efficacy (Center Panel)**
- **Dosing (Right Panel)**
- **Back Panel Highlights**
  - Reduction in Pain-Related Sleep Interference
  - Dosage Forms for Flexibility in Dosing
  - Oral Solution



NE186750

NEURONTIN (gabapentin)

Trileptal: New Safety Warnings



TRILEPTAL® (oxcarbazepine)

INDICATION

Trileptal is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children aged 4 to 16 years with epilepsy.

Trileptal does not have FDA approval for the treatment of any neuropathic pain condition.

SAFETY

WARNINGS

- Hyponatremia
- Patients who have had hypersensitivity reactions to carbamazepine have an approximately 25% to 30% chance of experiencing hypersensitivity to reactions with Trileptal

PRECAUTIONS

- Cognitive/neuropsychiatric adverse events, including:
  - Psychomotor slowing, difficulty with concentration, and speech or language problems
  - Somnolence or fatigue
  - Coordination abnormalities, including ataxia and gait disturbances
- Pregnancy category C

For sales colleagues' information only. Not to be copied, distributed, left behind, or used for detailing.

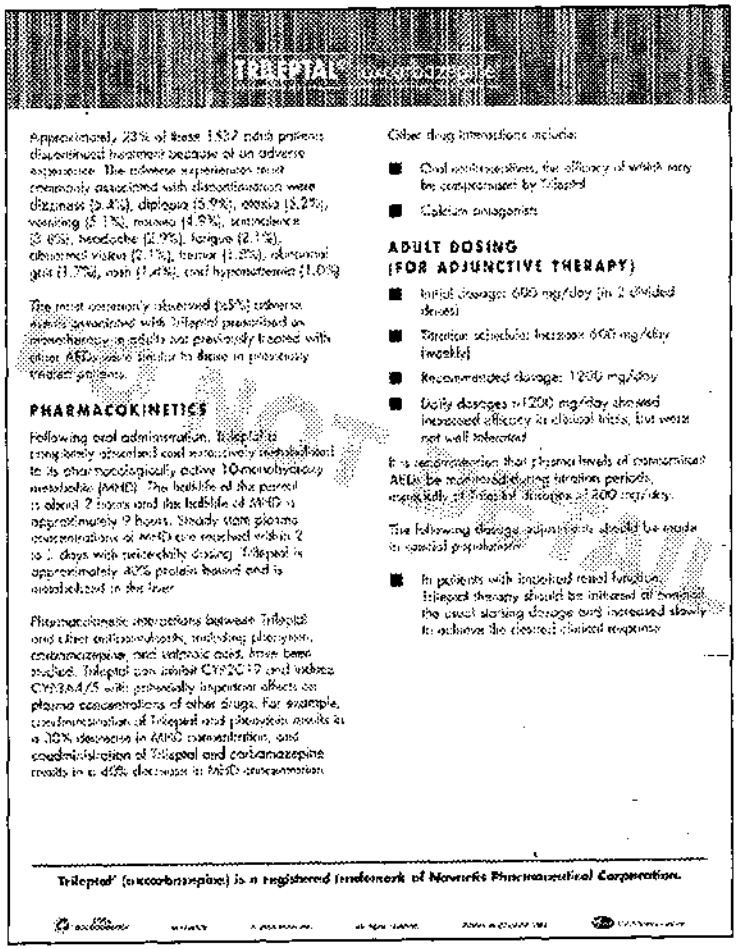
NE194670B

- **Indications in Addition to Epilepsy**
  - None
  - No FDA Approval for Any Type of Neuropathic Pain
- **Safety: Warnings**
  - Clinically Significant Low Sodium (Hyponatremia: Sodium <125 mmol/L) Can Develop During Trileptal Use
  - Label Recommends Monitoring of Serum Sodium Levels for All Patients
  - Patients Who Have Had a Hypersensitivity Reaction to Tegretol Have a 30-35% Chance of Experiencing Hypersensitivity to Trileptal

Implications:
Routine Monitoring of All Patients

NEURONTIN (gabapentin)

Trileptal: Many Drug Interactions



TRILEPTAL® (oxcarbazepine)

Approximately 28% of these 1,532 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were dizziness (3.4%), diplopia (3.9%), ataxia (3.2%), vomiting (3.1%), nausea (4.9%), somnolence (3.6%), headache (2.9%), fatigue (2.1%), abnormal vision (2.1%), tremor (1.2%), abnormal gait (1.7%), rash (1.4%), and hyponatremia (1.0%).

The most commonly observed (≥5%) adverse events associated with Trileptal prescribed as monotherapy in adults not previously treated with other AEDs were similar to those in previously treated patients.

PHARMACOKINETICS

Following oral administration, Trileptal is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). The half-life of the parent is about 2 hours and the half-life of MHD is approximately 9 hours. Steady state plasma concentrations of MHD are reached within 2 to 3 days with twice-daily dosing. Trileptal is approximately 40% protein bound and is metabolized in the liver.

Pharmacokinetic interactions between Trileptal and other antiepileptics, including phenytoin, carbamazepine, and valproic acid, have been studied. Trileptal can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs. For example, coadministration of Trileptal and phenytoin results in a 30% decrease in MHD concentration, and coadministration of Trileptal and carbamazepine results in a 40% decrease in MHD concentration.

Other drug interactions include:

- Oral contraceptives, the efficacy of which may be compromised by Trileptal
- Calcium antagonists

ADULT DOSING (FOR ADJUNCTIVE THERAPY)

- Initial dosage: 600 mg/day (in 2 divided doses)
- Titration schedule: Increase 600 mg/day (weekly)
- Recommended dosage: 1200 mg/day
- Daily dosages >1200 mg/day showed increased efficacy in clinical trials, but were not well tolerated

It is recommended that plasma levels of concomitant AEDs be monitored during titration periods, especially at Trileptal dosages >1200 mg/day.

The following dosage adjustments should be made in special populations:

- In patients with impaired renal function, Trileptal therapy should be initiated at one-half the usual starting dosage and increased slowly to achieve the desired clinical response.

Trileptal® (oxcarbazepine) is a registered trademark of Novartis Pharmaceutical Corporation.

NE194670B

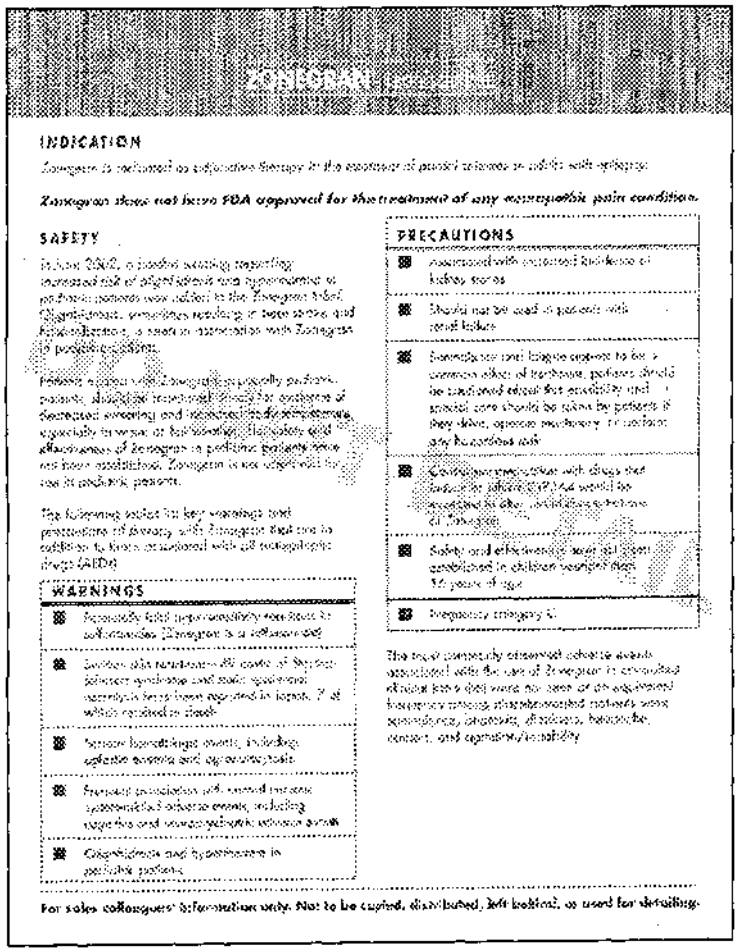
Significant Drug Interactions

- **Interacts Significantly with Other Common Anticonvulsants Like Phenytoin, Carbmazepine and Valproic Acid**
- **Trileptal Can Inhibit CYP2C19 and Induce CYP3A4/5 with Important Effects on Plasma Concentrations of Other Drugs**
- **Efficacy of Oral Contraceptives May Be Compromised**
- **Interactions with Calcium Antagonists**

Implications:
Many Drug-Drug Interactions

NEURONTIN (gabapentin)

Zonegran: New Safety Warnings



INDICATION

Zonegran does not have FDA approved for the treatment of any neuropathic pain condition.

SAFETY

PRECAUTIONS

WARNINGS

For sales colleagues' information only. Not to be copied, distributed, left behind, or used for detailing.

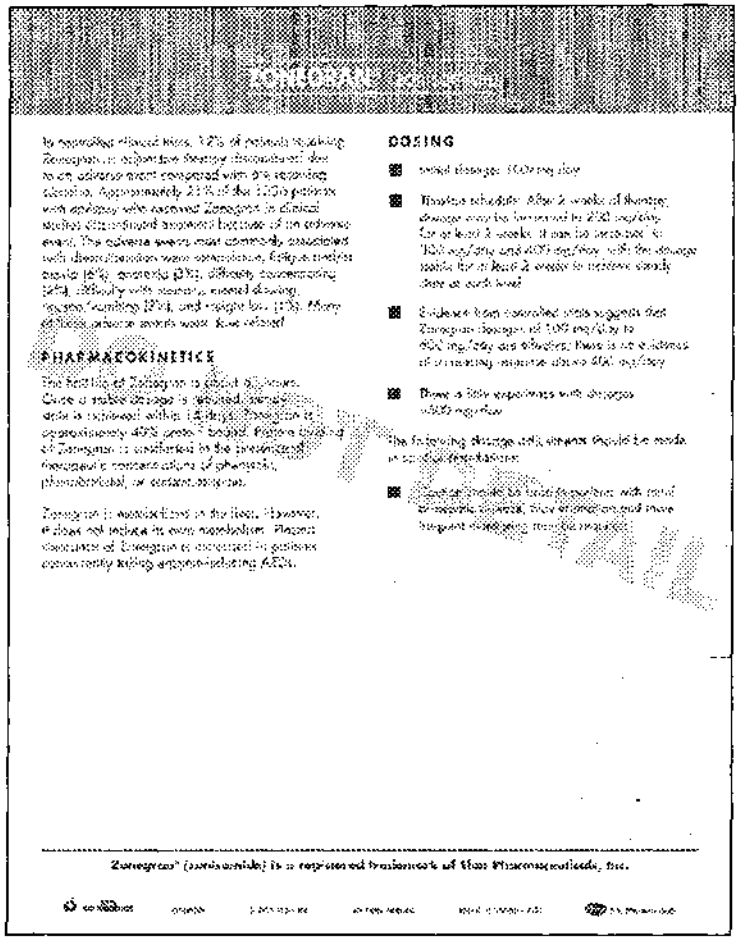
NE194670A

- **Indications: In Addition to Epilepsy**
  - **None**
  - **No FDA Approval for Any Type of Neuropathic Pain**
- **Warnings**
  - **Impaired Sweating (Oligohidrosis) and Hyperthermia in Pediatric Patients**
  - **Potentially Fatal Hypersensitivity to Sulfonamides (Zonisamide Is a Sulfonamide)**
  - **Serious Skin Reactions – 49 Cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, 7 of Which Resulted in Death**
  - **Serious Hematologic Events, Including Aplastic Anemia and Agranulocytosis**

Implications:
Potentially Disfiguring or Fatal Reaction

NEURONTIN (gabapentin)

Zonegran: Precautions and Important Drug Interactions



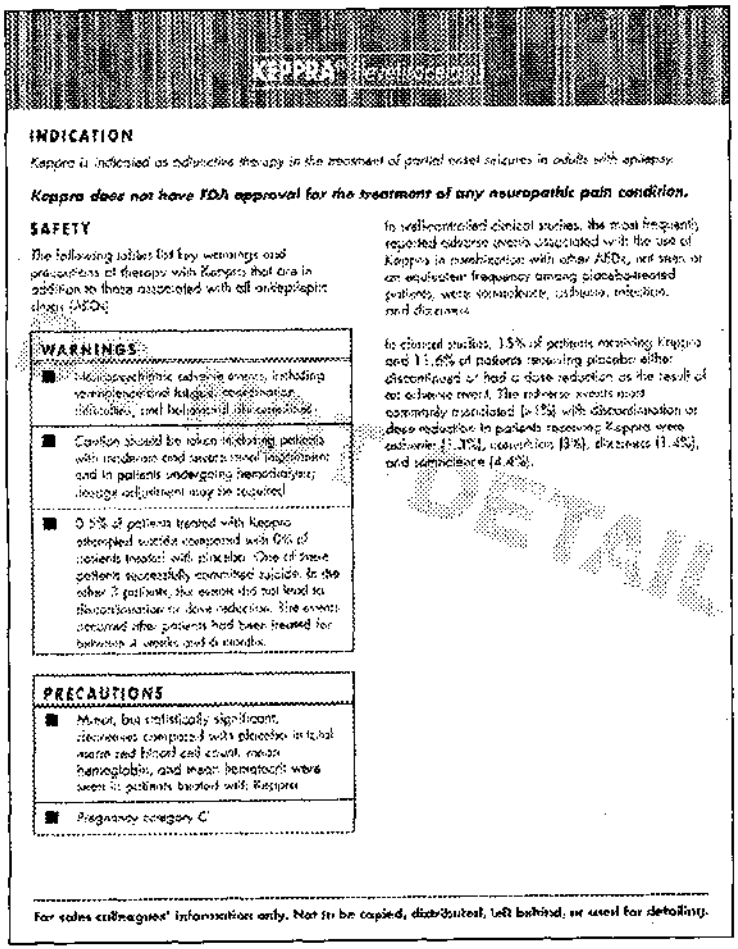
NE194670A

- **Precautions**
  - Associated with Increased Incidence of Kidney Stones
  - Should Not Be Used in Patients with Renal Failure
  - Somnolence and Fatigue Appear to Be a Common Effect of Treatment
  - Safety and Efficacy Not Established in Patients Under 16
- **Significant Drug Interactions**
  - Concurrent Medication with Drugs That Induce or Inhibit CYP3A4 Would Be Expected to Alter Concentrations of Zonegran
  - Plasma Clearance of Zonegran Is Increased in Patients Concurrently Taking Enzyme-Inducing AEDs

Implications:
Potentially Fatal and Many Drug-Drug Interactions

NEURONTIN (gabapentin)

Keppra: Warnings and Precautions



KEPPRA® (levetiracetam)

INDICATION

Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

Keppra does not have FDA approval for the treatment of any neuropathic pain condition.

SAFETY

The following tables list key warnings and precautions of therapy with Keppra that are in addition to those associated with all antiepileptic drugs (AEDs).

WARNINGS

- Psychopathic adverse events, including somnolence and fatigue, coordination difficulties, and behavioral abnormalities
- Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing hemodialysis; dosage adjustment may be required
- 0.5% of patients treated with Keppra attempted suicide compared with 0% of patients treated with placebo. One of these patients successfully committed suicide. In the other 3 patients, the events did not lead to discontinuation or dose reduction. The events occurred after patients had been treated for between 4 weeks and 6 months.

PRECAUTIONS

- Minor, but statistically significant, decreases compared with placebo in total white cell and lymphocyte counts, mean hemoglobin, and mean hematocrit were seen in patients treated with Keppra
- Pregnancy category C

In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra in combination with other AEDs, and seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection, and dizziness.

In clinical studies, 15% of patients receiving Keppra and 11.6% of patients receiving placebo either discontinued or had a dose reduction as the result of an adverse event. The adverse events most commonly associated (≥1%) with discontinuation or dose reduction in patients receiving Keppra were asthenia (1.3%), somnolence (3%), dizziness (1.4%), and convulsions (4.4%).

NE194670C

- **Indications in Addition to Epilepsy**
  - None
  - No FDA Approval for Any Type of Neuropathic Pain
- **Safety: Warnings**
  - Caution in Dosing Patients with Moderate and Severe Renal Impairment and in Patients Undergoing Hemodialysis
  - 0.5% of Patients with Keppra Attempted Suicide Compared with 0% of Patients Treated with Placebo. One of These Patients Successfully Committed Suicide

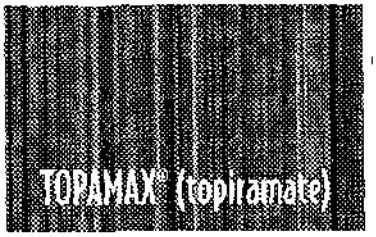
Implications:
No Demonstration of Efficacy in PHN and Suicide Warning

NEURONTIN (gabapentin)

Action: Use Competitive Backgrounder to

- **Highlight Warnings, Monitoring Requirements and Drug-Drug Interactions of Trileptal and Zonegran *IF AND ONLY IF* Physician Discusses These Drugs**
- **Highlight That Keppra, Trileptal and Zonegran *ARE NOT APPROVED* for the Treatment of Any Neuropathic Pain Condition *IF AND ONLY IF* Physician Discusses Use of These Drugs to Treat PHN**

February 9, 2004



INDICATION

Topamax is indicated as adjunctive therapy for adults and pediatric patients aged 2 to 16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age or older with seizures associated with Lennox-Gastaut syndrome.

An indication for prevention of migraine is expected in early 2004.

Topamax has no FDA approval for the treatment of any neuropathic pain condition.

SAFETY

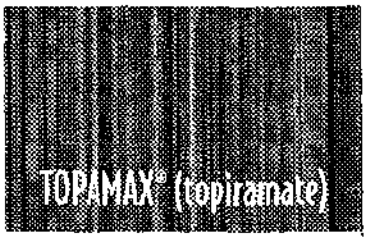
In December 2003, a warning regarding metabolic acidosis (decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) was added to the Topamax label. Previous labeling listed metabolic acidosis as an infrequent adverse event. However, the new warning recommends monitoring of serum bicarbonate during treatment with Topamax. Conditions that may predispose patients to acidosis include renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, and ketogenic diet.

In July 2003, a warning regarding the development of oligohidrosis (decreased sweating) and hyperthermia was added to the Topamax label. The new warning appears in 2 sections of the label. The first mention is a warning for oligohidrosis, which may lead to increased body temperatures because the patient's normal mechanism of cooling (sweating) may be diminished. The second mention warns about drug interactions with Topamax that may predispose a patient to oligohidrosis and hyperthermia.

The following table lists key warnings and precautions of therapy with Topamax that are in addition to those associated with all antiepileptic drugs (AEDs).

WARNINGS AND PRECAUTIONS
■ Metabolic acidosis
■ Oligohidrosis and hyperthermia
■ Risk of myopia associated with secondary angle closure glaucoma
■ Associated with a higher incidence of kidney stones
■ Paresthesia appears to be a common effect of treatment
■ Dosage adjustments may be required in patients with renal or hepatic impairment
■ Pregnancy category C

In clinical trials, 11% of patients who received Topamax 200 mg/day to 400 mg/day and approximately 28% of patients who received Topamax 200 mg/day to 1600 mg/day discontinued treatment due to adverse events.



Adverse events most often associated with Topamax were central nervous system (CNS) related. In adults, the most significant of these can be classified into 2 general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems; and 2) somnolence or fatigue.

The most common adverse events associated with the use of Topamax at dosages of 200 mg/day to 400 mg/day that were seen at greater frequency in patients receiving Topamax and did not appear to be dose-related were somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia, and diplopia.

The most common dose-related adverse events at dosages of 200 mg/day to 1000 mg/day were fatigue, nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems, and weight decrease.

PHARMACOKINETICS

The half-life of Topamax is 21 hours, and concentrations reach steady state in 4 days. Topamax is approximately 13% to 17% protein bound. Topamax is not extensively metabolized.

Pharmacokinetic interactions between Topamax and other anticonvulsants, including phenytoin, carbamazepine, and valproic acid, have been reported. For example, coadministration of Topamax and phenytoin results in a 48% decrease in Topamax concentration, and coadministration of Topamax and carbamazepine results in a 40% decrease in Topamax concentration. Other drug interactions include:

- CNS-depressant drugs, with which Topamax should be used with caution
- Oral contraceptives, the efficacy of which may be compromised by Topamax
- Other carbonic anhydrase inhibitors, which should be avoided by patients taking Topamax

ADULT DOSING (FOR ADJUNCTIVE THERAPY)

- Initial dosage: 25 mg/day to 50 mg/day
- Titration schedule: Increase by 25 mg/week to 50 mg/week
- Recommended total dosage: 400 mg/day
- Daily doses >1600 mg have not been studied

The following dosage adjustments should be made in special populations:

- In patients with renal impairment (creatinine clearance <70 mL/min/1.73 m^2), 50% of the usual dose is recommended
- Since Topamax is rapidly cleared in patients undergoing hemodialysis, a supplemental dose may be required to maintain antiseizure effect

February 9, 2004

LAMICTAL® (lamotrigine)

INDICATION

Lamictal is indicated as adjunctive therapy for partial seizures in adults and pediatric patients 2 years of age or older. Lamictal is also indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome in adults and pediatric patients 2 years of age or older. Lamictal is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single enzyme-inducing antiepileptic drug (AED). The safety and effectiveness of Lamictal have not been established in the following situations:

- *As initial monotherapy*
- *For conversion to monotherapy from non–enzyme-inducing anticonvulsant therapy (valproate)*
- *For simultaneous conversion to monotherapy from 2 or more concomitant anticonvulsants*

Lamictal is also indicated for maintenance treatment of Bipolar 1 Disorder (in patients treated for acute mood episodes with standard therapy).

Lamictal has no FDA approval for the treatment of any neuropathic pain condition.

BLACK BOX WARNING

The Lamictal labeling includes a black box warning about serious rashes requiring hospitalization and discontinuation of treatment that have been reported with the use of Lamictal. The incidence of these rashes is approximately 0.8% in pediatric patients (aged <16 years) receiving Lamictal as adjunctive therapy for epilepsy and 0.3% in adults on adjunctive therapy for epilepsy. There are suggestions that the risk of rash may be increased by coadministration of Lamictal and valproate.

In a prospectively followed cohort of 1983 pediatric patients with epilepsy taking adjunctive Lamictal, there was 1 rash-related death. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate.

Because the rate of serious rash is greater in pediatric patients than in adults, it bears emphasis that Lamictal is approved only for use in pediatric patients (aged <16 years) who have seizures associated with the Lennox-Gastaut syndrome or in patients with partial seizures.

Although benign rashes also occur with Lamictal, it is not possible to predict reliably which rashes will prove to be serious or life threatening. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring.

February 9, 2004

LAMICTAL® (lamotrigine)

SAFETY

The following table lists key warnings and precautions of therapy with Lamictal that are in addition to those associated with all AEDs.

WARNINGS AND PRECAUTIONS
■ Black box warning regarding serious rashes requiring hospitalization and discontinuation of treatment. Prior to initiation of treatment with Lamictal, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (eg, fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately
■ Hypersensitivity reactions, some fatal or life threatening have occurred; early manifestations may include fever and lymphadenopathy
■ Acute multiorgan failure, which in some cases has been fatal or irreversible, has occurred in patients taking Lamictal
■ Dosage should be reduced when added to a regimen that includes valproate
■ Should be used with caution in patients with diseases or conditions that may affect metabolism or elimination of Lamictal (such as renal, hepatic, or cardiac function impairment)
■ There have been reports of blood dyscrasias that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and rarely, aplastic anemia and pure red cell aplasia
■ Pregnancy category C

In clinical trials, approximately 11% of patients who received Lamictal as adjunctive therapy and 10% of patients who received Lamictal as monotherapy discontinued treatment due to adverse events. The most common adverse events associated with the use of Lamictal and not seen at an equivalent frequency among placebo-treated patients were dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash.

PHARMACOKINETICS

The half-life of Lamictal varies considerably (13 to 59 hours), depending on how many other—and which—AEDs a patient is taking. Changes in dosage produce proportional changes in concentration. Lamictal is approximately 55% protein bound. Lamictal is metabolized in the liver by glucuronidation (not by the cytochrome P-450 system), and the major metabolite is inactive.

Pharmacokinetic interactions between Lamictal and valproate can occur, causing reduced clearance of Lamictal. When administered with valproate, the dosage of Lamictal should be reduced. Lamictal can also interact with phenytoin and carbamazepine.

ADULT DOSING

■ Varies by condition and type of therapy

The following dosage adjustments should be made in special populations:

■ In patients taking a drug regimen that includes valproate, the dosage of Lamictal should be reduced

■ Since the metabolism or elimination of Lamictal may be affected by renal, hepatic, or cardiac function impairment, caution should be used in patients with 1 or more of these conditions

COMPETITION USED FOR PHN

CARBAMAZEPINE (Tegretol, Epitol, Carbatrol)

Carbamazepine is indicated for another type of neuropathic pain: trigeminal neuralgia. Carbamazepine has severe dermatologic reactions and hepatic effects. It also has a black box warning for aplastic anemia and agranulocytosis.

LAMICTAL

Although it has no indication, GSK has conducted clinical trials for the indication of neuropathic pain. Lamictal has a black box warning as it causes serious rashes. After extended use, it had toxicity in melanin-rich tissues, such as the eye. It cautions use in patients with conditions that affect metabolism and elimination. It also has 38% occurrence of dizziness as an adverse event.

TCAs (amitryptyline/nortriptyline)

Analgesic effects are independent of antidepressant effects and occur at lower doses. TCAs are used as first-line agents in all types of neuropathic pain except trigeminal neuralgia. However, the therapeutic effects of TCAs usually occur 4-6 weeks after therapy begins. Also, plasma levels of TCAs often have to be monitored.

OPIOIDS

Opioids are sometimes used in the treatment of neuropatic pain. However, the efficacy in trials is controversial. Opioids can cause problems with the respiratory, cardiac, GI, and urinary systems. Also, opioids are linked with drug dependance and psychologic effects.

NSAIDs (Cox 1 and 2 inhibition)

NSAIDs are not indicated for neuropathic pain. It is important to speak of the differences of neuropathic and nociceptive pain. Many physicians use neurontin with NSAIDs in patients where diagnosis is difficult.

TRAMADOL (Ultram)

Tramadol is not indicated for any type of neuropathic pain. Tramadol is used by physicians in the treatment of moderate pain. Although Ortho-NcNeil has conducted clinical research, there is no published data for the treatment of PHN.

LIDODERM PATCH

Lidoderm patch is indicated for the treatment of pain associated with PHN. It is a local anesthetic agent. Lidoderm patch causes localized reactions at the treatment site. It

must be applied only to intact skin. Also, eye exposure and mucous membrane exposure must be avoided.

CAPSAICIN

Capsaicin is indicated for the relief of neuralgias such as PHN and diabetic neuropathy. It is a topical analgesic derived from hot paprika or chili peppers. Capsaicin causes burning, stinging, redness, cough, and respiratory inflammation. This gives this treatment a lower amount of compliance. Also, it has warnings against eye exposure and use on broken or irritated skin.

NMDA RECEPTOR ANTAGONISTS (ketamine)

Ketamine is a parenteral general anesthetic. It is not indicated for the treatment of PHN. It produced intolerable local reactions and adverse events in two studies. It causes hallucinations, vivid dreams, and delirium symptoms.

CLONIDINE

Clonidine is not indicated for PHN. Although it has shown effectiveness in clinical trials, frequent and severe adverse events such as drowsiness, dry mouth, and dizziness limit it's use.

BENZODIAZEPINES (valium/xanax)

Benzofiazepines work by enhancing the activity of GABA. Although they have no indication for PHN, they have shown effectiveness in clinical studies. Benzodiazepines have the risk for developing dependence. They also have frequent adverse events such as fatigue and drowsiness.

Compare and Win

Lamictal Compare and Win

1.No indication for any type of neuropathic pain
2.Black box warning-Serious rashes
a.Possibly life threatening or disfiguring
b.Discontinuation may not prevent rash from becoming life threatening or disfiguring
3.Possible acute multiorgan failure(can be fatal and irreversible)
4.Inconsistent half life-varies from 13-59 hours
5.Drug-drug interactions-Valproate, phenytoin, and carbamazepine

Topamax Compare and Win
1.No indication for any type of neuropathic pain
2. Safety Warnings
   a.Decreased sweating
   b.Hyperthermia
   c.Metabolic acidosis
3.Drug-drug interactions
   a.Oral contraceptives may be compromised
   b.Other AEDs(e.g. Phenytoin and Carbamazepine)
   c.Use caution w/other CNS depressant drugs
4.Titration schedule-can take up to 4 months to get to recommended dosage
5.Dosage adjustment for renally or hepatically impaired

Trileptal Compare and Win
1. No indication for any type of neuropathic pain
2. Hyponatremia(low sodium) can develop with use
3. Sodium level monitoring w/all patients
4. Drug-drug interactions
   a. Other AEDs(Phenytoin, Carbamazepine, Valproic Acid)
   b. Cyp 3a4/5 inducer and Cyp2c19 inhibitor

c. Oral contraceptives may be compromised
d. Calcium Antagonists interactions

Zonegran Compare and Win

1. No indication for any type of neuropathic pain
2. Serious Skin Reactions(49 cases-7 resulted in deaths-Stevens-Johnson syndrome)
3. Can cause Aplastic Anemia and Agranulocytosis
4. Side effects-Somnolence, Fatigue, Kidney stone increase
5. No use in renal failure patients or patients under 16
6. Drug-drug
    a. Non substrates of CYP3a4(Inducer or Inhibitor) alter concentrations
    b. Plasma clearance increased with patients taking enzyme-inducing AEDs

Keppra Compare and Win

1. No indication for any type of neuropathic pain
2. Suicide warning
3. Caution with moderate and severe renally impaired patients(undergoing hemodialysis)

Neurontin Compare and Win

1. Indication for Epilepsy and Post Herpetic Neuralgia
2. Two pivotal studies showing pain reduction within 1 week(Rice and Rowbotham)
3. Not hepatically metabolized or protein bound
4. Few Drug-drug interactions
5. Improved sleep(Reduction in sleep interference)
6. Easy to titrate with NEW scored 600mg tablet

Neurontin

Objection Handler

I've tried Neurontin for the management of PHN and I don't think it works.

When dosed to 1800 mg Neurontin provides proven efficacy in reductions in pain as well as other outcome domains…

- Efficacy proven in Rice and Rowbothom→500 patients
- Efficacy in PHN as well as improvement in bodily pain, vitality and mental health
- Significant reductions in sleep interference

1800 mg seems to be a very high dose.

If I showed you data on Neurontin used at 2400 mg and 3600 mg would that ease your concerns?

- Dosed to 2400 mg and 3600 mg in pivotal trials.
- Titration completed in 2 or 3 weeks respectively.
- A/E's were mild to moderate and transient included somnolence, dizziness and peripheral edema.
- NO clinically significant drug interactions.

It's difficult to titrate Neurontin and the titration schedule seems confusing.

The PI is clear about how to initiate therapy, but does not provide specific titration direction. However, the dosing option chart allows…

- Patients can reach 1800 mg by day 16.
- Start with 300 mg and add 300 mg every 3 days.
- The 600 mg TID dose provides your patients with the benefits of proven efficacy—including improved pain scores, improvement in bodily pain, vitality and mental health.

I am concerned about dosing Neurontin to this dose in the elderly and renal impaired.

I understand your concern about balancing efficacy and safety, however if dosed properly these patients can benefit from Neurontin therapy…

- You can easily calculate the dosage for elderly patients with renal impairment from the PI—based on creatinine clearance.
- The average age of patients in the 3600 mg study was 73.

Is there an interaction between morphine and Neurontin?

I have data showing Neurontin and morphine are safe to use concomitantly…

- Our study shows Neurontin did not affect morphine pharmacokinetics or metabolism.
- Morphine however did affect Neurontin—by causing an increased absorption of Neurontin.
- For this reason it is important to monitor these patients for CNS depression and to reduce the dose of morphine or Neurontin if necessary

How should I use Neurontin in the treatment of diabetic neuropathy, trigeminal neuralgia or "itchy toe syndrome?"

For information on that topic please call Pfizer Headquarters at 1-800-223-0432

- Neurontin has demonstrated efficacy and safety in 2 clinical trial in the management of PHN and in 4 trials for its indication as adjunctive therapy for partial seizures.

TCA's are cheaper than Neurontin and just as effective in the treatment of neuropathic pain.

If you are looking for a safe, effective treatment for PHN, Neurontin is the only oral FDA-approved therapy available.

- Neurontin demonstrated efficacy and safety for the management of PHN in two large placebo controlled clinical trials.
- Patient experienced
  - Significant pain relief
  - Improvement in vitality
  - Improvement in mental health
  - Reductions in sleep disturbances

I use opiods or NSAIDs (misdiagnosing PHN?)

NSAIDs and opiods are effective for many types of pain…

- Musculoskeletal pain arises from damage to tissue and neuropathic pain usually arises from injury or dysfunction of the nervous system.
- PHN pain arises from this type of damage to the nervous system
- In studies Neurontin provided significant pain relief to these patients—making it the only FDA-approved oral med for PHN

What does sleep interference mean and isn't it just a result of somnolence?

Patients with PHN may suffer significant sleep interference…

- Neurontin was shown to significantly reduce sleep interference PHN patients from baseline to the end of the study
- Drowsiness occurred in less than 25% of patients and is a measure of often affects patients during the day
- Sleep interference is however a measure of how well patients sleep at night
- Sleep architecture is improved with Neurontin

My primary concern is the pain of PHN—I find patient-reported data to be less relevant to my patients.

Pain is the most important outcome of our studies doctor…

- PHN pain can be so debilitating that it can interfere with daily activities.
- In two different trials we used a self administered questionnaire that measures 8 outcome domains
- Patients reported improvement in several domains including bodily pain, vitality and mental health
- Can you see how important patient-reported outcome domains are to your patients with PHN?

DO NOT DETAIL

January 12, 2004

To: Sales Managers and Representatives

From: NEURONTIN DMT

Re: Inquiries arising from class action advertisements

As you probably know, numerous advertisements are running nationwide seeking plaintiffs for a possible NEURONTIN® class action lawsuit. The advertisements, placed by lawyers and appearing on television, radio, and in newspapers, seek patients who have taken NEURONTIN and who have had suicidal thoughts/suicidal ideation. These ads have generated substantial concern among patients — some even have asked their physicians to take them off NEURONTIN. We believe that the ads are the result of the intense publicity surrounding NEURONTIN over the past year. The purpose of this communication is to provide you with information so that you know how to appropriately handle questions you may receive from health care professionals.

- **What has occurred to date with NEURONTIN?**

At this time, Pfizer is not aware of any legal claim or any lawsuit, whether a class action or not, that has been filed on behalf of anyone claiming to have suffered suicidal thoughts/suicidal ideation after taking NEURONTIN. It appears that the lawyers who are running the ads are trolling for prospective plaintiffs.

- **What are the NEURONTIN data with regard to suicidal ideation/suicidal attempts/suicide?**

Pfizer is committed to monitoring the safety of our products even after product approval. The NEURONTIN clinical database covers trials involving more than 2000 subjects. In subjects with neuropathic pain, in particular with PHN (600 subjects), there were no related reports in gabapentin-treated patients. In subjects with epilepsy, suicidal thoughts were reported as an infrequent adverse event and suicide gesture was reported as a rare adverse event.

- **How should sales representatives respond to safety questions about NEURONTIN?**

As always, your response to questions about our products must strictly conform to and be consistent with the package insert. NEURONTIN has almost 10 years of experience covering over 10 million patients and has been proven to be effective and ***well-tolerated*** in the management of postherpetic neuralgia patients and as adjunctive therapy in the treatment of partial seizures.

DO NOT DETAIL

Q & A on the safety of NEURONTIN® (gabapentin) regarding suicidal behaviors

I. SUMMARY

- NEURONTIN is indicated:
  - As adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients older than 12 years of age with epilepsy.
  - As adjunctive therapy in the treatment of partial seizures in pediatric patients 3 to 12 years of age.
  - For the management of postherpetic neuralgia (PHN) in adults.

- In clinical trials, NEURONTIN was administered to 2074 patients older than 12 years of age during epilepsy trials, some of which were placebo-controlled. *Suicidal thoughts* were reported as *infrequent (happening in 1 out of every 100 to 1 out of every 1000 patients)* and *suicide gesture* was reported as *rare (happening in fewer than 1 out of every 1000 patients)* in both adults and adolescents with epilepsy during clinical trials.

- There were no reports of suicide in the PHN trials.

- The presence of mental illness is a significant risk factor for suicidal behavior. Patients with chronic medical illnesses such as epilepsy, diabetes mellitus, and chronic pain have a higher incidence of depression than found in the general population. Hence the patients receiving NEURONTIN are part of this group that is already at higher risk for an underlying mood disorder that makes them vulnerable to the potential for suicidal behavior.

- We have received spontaneous reports of suicide or suicidal thoughts since the market introduction of NEURONTIN. Please note that these reports cannot be used to calculate incidence, estimates of risk, or whether or not taking NEURONTIN is responsible for suicide or suicidal thoughts.

- No relationship between the use of NEURONTIN and suicidal behavior has been established.

- The FDA has found no reason to take any action in response to these reports.

DO NOT DETAIL

I. Clinical and Epidemiological Overview of Suicide

1. What is the definition of suicide and suicidal ideation or thoughts?

Suicide is defined as the act of taking one's own life. While there is no consistent or common name or classification for suicidal acts, the diagnostic and statistical manual of mental disorders (DSM-IV) includes them as symptoms or signs that may be seen in major depression and borderline personality.[1]

Suicidal ideation, or thinking about committing suicide, can include several behaviors ranging from suicidal gestures, voicing of ideas, suicide plans, or risky lifestyles to nonfatal but injurious behavior with the intention to cause death (referred to as either a suicide attempt or parasuicide).[2]

2. How are suicidal thoughts evaluated?

Currently there is no standard way of evaluating suicidal thoughts. In many cases, for patients to be hospitalized, many managed care protocols require that suicidal thoughts not only be documented, but that there be a previous suicide attempt or formulated plan of suicide. The validity of these criteria is debated, however, because most serious attempts at suicide appear to be impulsive.[3]

3. How many suicides happen annually in the US?

There are approximately 30,000 suicides annually in the US or 12 out of every 100,000 Americans per year take their own lives, yielding a national percentage of 1.3% per year.[4]

4. What special populations are at high risk for suicidal behavior?

The presence of mental illness is a significant risk factor for suicidal behavior. Of the adults who commit suicide, as many as 90% have at least 1 psychiatric illness, most often depression, bipolar disorder, schizophrenia, substance abuse, or borderline personality disorder.[2] In addition, as the severity of depression increases, so does the risk of death by suicide. Furthermore, patients with chronic medical illnesses such as epilepsy, diabetes mellitus, and chronic pain also have a high incidence of depression.[5]

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II. NEURONTIN® (gabapentin) AND REPORTS OF SUICIDE

1. Is there a link between NEURONTIN and suicidal behavior?

No relationship between the use of NEURONTIN and suicidal behavior has been established.

It should be remembered that the patient population being prescribed NEURONTIN is part of a group of patients that is already at higher risk for an underlying mood disorder that makes them vulnerable to the potential for suicidal behavior. Chronic medical illnesses, such as epilepsy and chronic pain, are associated with a high risk of depression, which is most often linked to suicidal behavior.[5,6]

To date, there have been no case reports of suicidal behavior in elderly patients who were prescribed NEURONTIN for PHN.

2. Has suicide or suicidal thoughts (ideations) been reported in clinical trials of NEURONTIN?

In clinical trials, adverse events are recorded without regard to their cause.

NEURONTIN was administered to 2074 patients older than 12 years of age during adjunctive therapy clinical trials in epilepsy, some of which were placebo-controlled. There were 2 patients (0.096%) with suicide gesture and 6 patients (0.29%) who were suicidal (7 patients in total, 1 patient experienced both events). The frequencies shown in Table 1 represent the number of those patients exposed to NEURONTIN who experienced suicidal thoughts or gestures on at least 1 occasion while receiving treatment with NEURONTIN.[7]

As per our FDA-approved package labeling for NEURONTIN, *suicidal thoughts* were reported as an *infrequent event (happening in 1 out of every 100 to 1 out of every 1000 patients)* and *suicide gesture* was reported as a *rare event (happening in fewer than 1 out of every 1000 patients)* in both adults and adolescents with epilepsy during clinical trials. There were no reports of suicide in the PHN trials.[8]

DO NOT DETAIL

Table 1. Reports of Suicidal Thoughts and Suicide Gesture in NEURONTIN® (gabapentin) Clinical Trials of Patients With Epilepsy or PHN[7]

	Epilepsy			PHN			
	Placebo-controlled adjunctive therapy trials in patients >12 years of age[7,8]		In clinical trials*[,7,8]	Placebo-controlled trials in adults[7,8]		In pivotal controlled clinical trials in adults†[,7]	
	Gabapentin (N=543)	Placebo (N=378)	Gabapentin (N=1486)	Gabapentin (N=336)	Placebo (N=227)	Gabapentin (N=820)	Placebo (N=537)
Suicidal Thoughts	0	0	5 (0.3%)	0	0	0	0
Suicide Gesture	0	0	2 (0.1%)	0	0	0	0

* These controlled and uncontrolled studies included 1486 patients with epilepsy who received gabapentin therapy. Patients with migraine or spasticity were also included.

† These 5, double-blind, placebo-controlled, multicenter trials were conducted in patients with diabetic peripheral neuropathy, PHN, and mixed neuropathic pain.

3. Has suicide or suicidal thoughts been reported in postmarketing or safety surveillance data of NEURONTIN?

A search of our postmarketing safety surveillance database for NEURONTIN revealed that we have received spontaneous reports of suicide or suicidal thoughts since the market introduction of NEURONTIN. Accumulated spontaneous reports cannot be used to calculate incidence, estimates of risk, or whether or not taking NEURONTIN is responsible for suicide or suicidal thoughts because of the following reasons:

- Spontaneous reports are submitted on a voluntary basis and so the number of reports received may not reflect the actual number of cases that have occurred
- The actual number of patients receiving NEURONTIN at any given time is not known
- While case reports of suicidal behavior of patients taking NEURONTIN have been reported, the cause of the suicidal behavior or thoughts has not been established.

Pfizer Inc does not have any recommendations regarding the management of suicidal thoughts in patients receiving NEURONTIN.

4. Among case reports of patients who experienced suicidal behavior while taking NEURONTIN, what was the underlying medical condition for which NEURONTIN was prescribed? Were they prescribed other medications?

As of October 2003, a computerized search of the medical literature has identified case reports of suicidal behavior and the use of NEURONTIN.

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A published study of gabapentin-only exposures from April 1, 1998 to April 1, 2000 reported to 3 poison control centers revealed a total of 20 cases reported, 11 of which were an intentional suicide attempt, 5 were a result of therapeutic error, and 4 were listed as "unintentional general."[9]

Of the case reports published in the literature, a review of the patient medical histories show that 3 of the patients were epileptic, 1 had type 2 diabetes, and 1 had schizoaffective disorder.[10–14] The patient with type 2 diabetes had attempted suicide previously and was taking an antipsychotic and an antidepressant in addition to NEURONTIN. All 3 epileptic patients were taking other antiseizure medications, and 1 of these patients also had concomitant alcohol exposure. In all cases, the overdose was treated with gastric lavage and recovery was uneventful. There were no deaths.[10–14]

DO NOT DETAIL

III. NEURONTIN® (gabapentin) PRESCRIBING AND REGULATORY INFORMATION

1. What are the indications for NEURONTIN?

NEURONTIN is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients older than 12 years of age with epilepsy. NEURONTIN is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients 3 to12 years of age.[8]

NEURONTIN is also indicated for the management of postherpetic neuralgia in adults.[8]

NEURONTIN is not approved by the Food and Drug Administration (FDA) for other medical or psychiatric conditions. Therefore, Pfizer Inc does not suggest or recommend the use of NEURONTIN for conditions other than partial epileptic seizures or PHN.

2. Has the FDA been informed of these incidents?

Yes. A MedWatch form must be filled out with the admitting diagnosis, detailed patient history and diagnosis, and all concomitant medications, which would include prescription or nonprescription drugs, as well as alcohol and so on.

3. What action is being taken by the FDA in response to these incidents?

The FDA has found no reason to take any action in response to these reports. The FDA has approved NEURONTIN as safe and effective as an adjunctive treatment for partial seizures in epilepsy patients and the pain associated with PHN.

4. Are there currently any studies underway involving NEURONTIN?

In the US, Pfizer is sponsoring a placebo-controlled trial to determine the efficacy of NEURONTIN in painful diabetic neuropathy.

DO NOT DETAIL

IV. Patient Safety Information

1. Who is at risk of suicide?

Up to 90% of adults who commit suicide have been diagnosed with at least 1 psychiatric disorder as classified by the DSM-IV, the most prevalent of which is major depression.[2] Patients with chronic medical illnesses, such as epilepsy and chronic pain like that associated with PHN, have a high prevalence of depression. The progressive loss of function and impairment associated with a chronic illness may cause depression, and several studies show that suicidal behavior is commonly found in chronic pain populations.[5,6]

In addition, an assessment of risk in managed care showed that 84% of the patients studied contacted some type of healthcare provider within the month before their suicide attempt.[3] Thus, the opportunity exists for a physician to evaluate and treat patients in these high-risk groups.

2. What percent of NEURONTIN® (gabapentin) patients have committed suicide who were prescribed other treatments, such as opioids, for PHN?

No PHN patients committed suicide.